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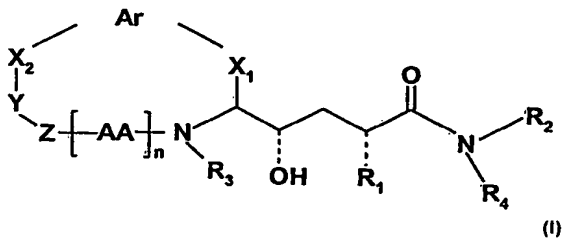
(54) Title: MACROCYCLIC COMPOUNDS HAVING ASPARTIC PROTEASE INHIBITING ACTIVITY AND PHARMACEUTICAL USES THEREOF



(I)

(57) Abstract: The present invention relates to macrocyclic compounds of formula (I), wherein R_1, is (C_{1-8})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, hydroxy(C_{1-6})alkyl, (C_{1-4})alkylthio(C_{1-4})alkyl, (C_{1-6})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, piperidinyl or pyrrolidinyl, R_2 and R_4, independently, are hydrogen or optionally substituted (C_{1-8})alkyl, (C_{3-7}) cycloalkyl, (C_{3-7})cycloalkyl(C_{1-4})alkyl, aryl, aryl(C_{1-4})alkyl, heteroaryl or heteroaryl(C_{1-4}) alkyl, or R_2 and R_4, together with the nitrogen to which they are attached, form an optionally substituted piperidino, pyrrolidinyl, morpholino or piperazinyl group, R_3 is hydrogen or (C_{1-4})alkyl, X_1 is CH_2, X_2 is CH_2, O, S, CO, COO, OCO, NHCO, CONH, or NR, R being hydrogen or (C_{1-4})alkyl, Y is (C_{1-8})alkylen or (C_{1-8})alkylenoxy(C_{1-6})alkylen, (C_{1-8})alkenylen or (C_{1-8})alkenylenoxy(C_{1-6})alkylen, Ar is a phenyl ring optionally mono- di or trisubstituted by, independently, hydroxy or halogen, whereby X_1, and X_2 are in meta or para position to each other, and either Z is CO, AA is a natural or unnatural alpha-amino-acid, and n is 0 or 1, or Z is SO_2, AA is an optionally substituted ethylencarbonyl group (derived from a natural or unnatural alpha-amino acid by replacement of the nitrogen by a methylen group), and n is 1; processes for the preparation of these compounds; pharmaceutical compositions and combinations comprising the same; and their use in the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

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